Neonatal Respiratory Distress Syndrome: Tackling A Worldwide Problem

Janet Dyer

It's the 21st century, yet newborn infants are still at risk for a deadly condition that robs them of their first breaths: neonatal respiratory distress syndrome (NRDS), also known as infant respiratory distress syndrome and hyaline membrane disease (*see videos listed in Box 1: Can You Identify NRDS?*). In countries with large pockets of poverty, mortality rates run roughly 10 times higher than in wealthier countries. But even in developed countries, the mortality rate reaches as high as 60%.[1] In the U.S., respiratory distress syndrome is among the most common causes of death in the first month of life.[2]

NRDS is also a threat for different reasons. For example, in one recent study, 1.9% of premature babies who had NRDS later developed cerebral palsy, compared with 0.5% of premature babies who did not have NRDS.[3] A 2018 study found premature infants had a higher risk of childhood epilepsy.[4]

Moreover, the treatments for NRDS have risks of their own. Mechanical ventilation, for instance, which helps keep infants alive, also puts them at risk for bronchopulmonary dysplasia (BPD). An estimated 5,000 to 10,000 newborns develop BPD or other form of chronic lung disease.[5]

However, more babies are surviving RDS. A main breakthrough has been the development of surfactant replacement, now the go-to therapy. Its use has meant an astounding drop in mortality, from nearly 100% to less than 10%.[5,6] Various researchers seek to polish that gold standard by finding the best timing, best dose, and best methods of delivering surfactant treatment to maximize effect and minimize risks.[7] A 2017 study, for instance, found early treatment with pulmonary surfactant—within 12 hours of birth—combined with mechanical ventilation could "remarkably improve lung oxygenation and compliance."[8]

Another mainstay of treatment for NRDS, inhaled nitric oxide, improves oxygenation and reduces pulmonary inflammation. Begun soon after birth in premature infants, it relieves acute symptoms and helps reduce the risk of chronic lung disease.[5] It's indicated for term and near-term (> 34 weeks' gestation) infants,[9] but some physicians are prescribing it for extremely premature infants. That practice has caused debate; in one study, giving iNO off-label did not reduce in-hospital mortality.[10]

Curious about current protocols? The American Academy of Pediatrics Committee on Fetus and Newborn has a list of guidelines, including those citing Cochrane Neonatal Reviews.[11]

WHAT'S NEXT? TRENDS IN TREATMENT

A review of the state of the art in treatment for NRDS says there's more work to be done. Recently, research has focused more on making treatment less invasive and more targeted. For example, new evidence has demonstrated that selective use of surfactant, rather than prophylactic use, reduces BPD and/or death.[7]

Another proposition is to administer surfactant differently: Using a small catheter, for instance, instead of an endotracheal tube for infants breathing spontaneously may combine the benefits of continuous positive airway pressure (CPAP) (thus avoiding mechanical ventilation) and early surfactant treatment.[7] Other research suggests that nebulized surfactant may reduce the need for intubation in preterm infants treated with nasal CPAP.[12]

Researchers are also looking to revise protocols on mechanical ventilation and oxygenation. A small pilot study published earlier this year suggests that even a short period under invasive mechanical ventilation at higher oxygen levels can lead

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Can You Identify NRDS?

Video: Respiratory Distress in the Newborn by Megan Connelly for OPENPediatrics. Differential diagnosis, epidemiology, pathophysiology, presentation, diagnosis, management
9:54 min
https://www.youtube.com/watch?v=j3ypUlLMRLs

Video: Recognizing Respiratory Distress by Monica Kleinman, MD, for OPENPediatrics.
Identifying signs and symptoms in the pediatric patient
17:24 min
https://www.youtube.com/watch?v=Fmt6JB-W_M8

Newborn Respiratory Disorders—CRASH! Medical Review Series
30:12 min
https://www.youtube.com/watch?v=KEd0EvbKjf8

The Stats on NRDS

- About 1% of newborn infants develop respiratory distress syndrome.
- About 12% of babies born in the U.S. are born prematurely—a higher rate than in other developed countries.
- Preterm birth is the world's number-one cause of newborn deaths (almost 30%).
- Neonatal respiratory distress syndrome is the leading cause of death in premature infants.
- The risk of RDS depends on gestational age: > 50% at < 28 weeks; < 5% at > 37 weeks.
- Between 2003 and 2013, the number of deaths due to NRDS dropped from 20.5 per 100,000 live births to 13.4.
- NRDS accounted for 2.3% of all infant deaths in the U.S. in 2013.

Sources:
AMBOSS.com. Neonatal Respiratory Distress Syndrome
March of Dimes Peristats[18]
American Thoracic Society. Respiratory Distress Syndrome of the Newborn, Chapter 19

to lung inflammation: higher IL-6, IL-8, and TNF-α levels and lower IL-10 levels.[13]

Some research is focusing on nutrition. Vitamin D, for instance, has been shown to help stimulate fetal lung maturation; deficiency in the vitamin lowers oxygenation and reduces survival time in preterm neonates.[14] Vitamin A, important to cell growth, has been shown to reduce BPD.[4]

Other recent trends in modern neonatology include revisiting standard ideas. Some of the questions being considered include:

- Should antenatal corticosteroids be routine?[15]
- Is nasal respiratory support a safe and efficient alternative to endotracheal ventilation in premature infants?[15]
- Is the assumption that nasal CPAP is less invasive and less injurious to the lung than endotracheal ventilation incorrect? Is nasal cPAP being overused?[16]

But while treatments have improved by leaps and bounds, they have not been able to keep up with the ever-growing incidence of preterm birth, by far the biggest risk factor for NRDS. According to the American Thoracic Society, "Preventing premature births could nearly eliminate RDS."[5]

In the meantime, research and experimentation continue around the globe, especially in countries that are high in preterm births and low in resources like ventilators and CPAP. In those places, desperate times are leading to innovative measures. In Malawi, for instance, where babies with RDS have only a 25% chance of survival, the existing medical devices tend to break down under the harsh conditions of African health care settings. So, doctors there competed in a design challenge and created a more affordable and durable bubble-CPAP. Their prototype? A plastic shoebox from Target and two fish-tank pumps. It cost a fraction of the price of the real CPAP but proved just as effective. With the help of engineering professors from Rice University, they perfected their device and called it *Pumani*—Malawian for "breathe restfully."[17]

Pioneer in Treatment of Neonatal Respiratory Distress Dies

In 1963, Jacqueline Kennedy gave birth to a baby nearly six weeks early. Within minutes, the baby, Patrick Bouvier, began struggling to breathe. He was rushed to Boston Children's Hospital, where he was placed in a hyperbaric chamber—a revolutionary treatment at the time.

Standing by was William F. Bernhard, a cardiovascular surgeon at Children's Hospital, and already a leader in the use of hyperbaric chambers in medicine. Bernhard made more medical history as he and the medical team attempted to save the baby's life.

Patrick died two days later of hyaline membrane disease, now called neonatal respiratory distress syndrome. The case, with all the media attention, heightened public awareness of the disease and spurred further research.

Patrick Kennedy's obituary in *The New York Times* read, in part: "[T]he battle for the Kennedy baby was lost only because medical science had not yet advanced far enough to accomplish as quickly as necessary what the body can do by itself in its own time."[5]

Dr. Bernhard died on October 29, 2018, aged 93.[19]

REFERENCES

1. Hubbard RM, Choudhury KM, Lim G. Treatment patterns and clinical outcomes in neonates diagnosed with respiratory distress syndrome in a low-income country: a report from Bangladesh. *Anesth Analg* 2018;5(126):1684–1686. doi: 10.1213/ANE.0000000000002865.
2. Jacob J, Kamitsuka M, Clark RH, Kelleher AS, Spitzer AR. Etiologies of NICU deaths [published online December 8, 2014]. *Pediatrics* 2015;135(1):e59–e65. doi:10.1542/peds.2014-2967.
3. Thygesen SK, Olsen M, Østergaard JR, et al. Respiratory distress syndrome in moderately late and late preterm infants and risk of cerebral palsy: a population-based cohort study. *BMJ Open* 2016;6:e011643. Available at: https://bmjopen.bmj.com/content/6/10/e011643. Accessed January 9, 2019.
4. Thygesen SK, Olsen M, Pedersen L, et al. Respiratory distress syndrome in preterm infants and risk of epilepsy in a Danish cohort [published online September 8, 2017]. *Eur J Epidemiol* 2018;33(3):313–321. doi: 10.1007/s10654-017-0308-1.
5. American Thoracic Society. Respiratory distress syndrome of the newborn. Available at: https://www.thoracic.org/patients/patient-resources/breathing-in-america/resources/chapter-19-respiratory-distress-syndr.pdf. Accessed January 4, 2019.
6. Mandile O. Neonatal respiratory distress syndrome and its treatment with artificial surfactant. The embryo project encyclopedia. The embryo project at Arizona State University. July 3, 2018. Available at: https://embryo.asu.edu/pages/neonatal-respiratory-distress-syndrome-and-its-treatment-artificial-surfactant. Accessed January 4, 2019.
7. Niemarkt HJ, Hütten MC, Kramer BW. Surfactant for respiratory distress syndrome: new ideas on a familiar drug with innovative applications. *Neonatology* 2017;111(4):408–414. doi: 10.1159/000458466.
8. Wang L.-P, Mao Q.-H, Yang L. Effect of pulmonary surfactant combined with mechanical ventilation on oxygenation functions and expressions of serum transforming growth factor-beta1 (TGF-β1) and bone morphogenetic protein 7 (BMP-7) of neonatal respiratory distress syndrome. Eur Rev Med Pharmacol Sci 2017;21(19):4357–4361. Accessed January 9, 2019.
9. Inomax (nitric oxide) prescribing information. Hazelwood, Montana: INO Therapeutics LLC; 2015.
10. Carey WA , Weaver AL , Mara KC , Clark RH. Inhaled nitric oxide in extremely premature neonates with respiratory distress syndrome [published online February 2, 2018]. *Pediatrics* 2018;141(3):e20173108. doi: 10.1542/peds.2017-3108.
11. Cochrane Neonatal. American Academy of Pediatrics Committee on Fetus and Newborn. January 2019. Available at: https://neonatal.cochrane.org/our-work/guidelines/american-academy-pediatrics-committee-fetus-and-newborn#surfactant. Accessed January 4, 2019.
12. Minocchieri S, Berry CA, Pillow JJ. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial [July 26, 2018]. *Arch Dis Child Fetal Neonatal Ed* 2018; pii: fetalneonatal-2018-315051. doi: 10.1136/archdischild-2018-315051.
13. Carvalho CG, Procianoy RS, Neto EC, Silveira RC. Preterm neonates with respiratory distress syndrome: ventilator-induced lung injury and oxidative stress. *J Immunol Res* 2018;6963754. doi: 10.1155/2018/6963754.
14. Gatera VA, Abdulah R, Musfiroh I, et al. Updates on the status of vitamin D as a risk factor for respiratory distress syndrome. *Adv Pharmacol Sci* 2018;8494816. doi: 10.1155/2018/8494816.
15. Kugelman A, Borenstein-Levin L, Jubran H, et al. Less is more: modern neonatology [July 30, 2018]. *Rambam Maimonides Med J* 2018;9(3):e0023. doi:10.5041/RMMJ.10344.
16. Doyle LW, Carse E, Adams A-M, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017;377(4):329–337. doi: 10.1056/NEJMoa1700827.
17. Dahl C. The vital role of early-innovation funders. *Stanford Social Innovation Review* 2019. Available at: https://ssir.org/articles/entry/the_vital_role_of_early_innovation_funders. Accessed January 4, 2019.

18. March of Dimes. Peristats. Available at: https://www.marchofdimes.org/search-results.aspx?search-text=Peristats. Accessed January 4, 2019.
19. Marquard B. Dr. William F. Bernhard, innovative surgeon who treated baby Patrick Kennedy, dies at 93. *Boston Globe*. November 2, 2018. Available at: https://www.bostonglobe.com/metro/obituaries/2018/11/01/william-bernhard-innovative-surgeon-who-treated-baby-patrick-kennedy-dies/qBKotnya3xxj90TmKCZHAI/story.html. Accessed January 4, 2019. ■

Newborn News

Topical Antibiotic Eradicates *S. Aureus* in NICU Infants

Applying mupirocin, a topical antibiotic, to various body areas safely and effectively eliminates *Staphylococcus aureus* (SA) colonization on infants in the neonatal intensive care unit (NICU), according to researchers.

University of Maryland researchers conducted a phase 2 multicenter, open-label, randomized trial assessing the safety and efficacy of intranasal plus topical mupirocin (Bactroban, GlaxoSmithKline; Centany, Medimetriks Pharmaceuticals Inc) in decolonizing SA in critically ill infants between April 2014 and May 2016.

S. aureus is a leading cause of sepsis in young children admitted to the NICU, and for infants, sepsis can prove fatal. Preventing such infections is extremely important for NICU babies, who are delicate and are often fighting multiple medical issues.

Infants in NICUs at eight study centers, aged younger than 24 months and colonized with SA, were randomly assigned to receive 5 days of mupirocin versus no mupirocin to the intranasal, periumbilical, and perianal areas. Treatment effects for all areas were evaluated on day 8 (primary decolonization) and day 22 (persistent decolonization). Primary decolonization occurred in 62/66 (93.9%) of treated infants and 3/64 (4.7%) of the control infants ($P < 0.001$). Persistent decolonization was seen in 21/46 (45.7%) of treated infants compared with 1/48 (2.1%) of the controls ($P < 0.001$).

Source: MDedge.com, January 3, 2019

Blood/Genetic Tests Can Identify Leukemia Risk in Newborns with Down Syndrome

Research into hundreds of babies with Down syndrome is providing valuable insight into leukemia's genetic roots and offering a route to identify newborns at high risk.

A study by researchers at the University of Oxford's MRC Weatherall Institute of Molecular Medicine identified children at high risk of developing myeloid leukemia within four years through blood or genetic tests.

Approximately 2%–3% of children with Down syndrome develop acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML) at a far higher rate than that of the general population. In children aged 0–4 years with Down syndrome, AML's standardized incidence ratio (SIR) is 114, compared with other children. The SIR of ALL is 27 in children aged 1–4 years.

The study recruited 471 neonates with Down syndrome and followed them for up to four years. One focus was on AML that appears before age 4 and is preceded by a neonatal preleukemia – transient abnormal myelopoiesis (TAM) – that only occurs in Down syndrome. TAM, which occurs with GATA1 mutations, usually resolves on its own after birth. But sometimes, the mutations continue, causing AML to develop.

The study showed that 341 of the children had no GATA1 mutation and 130 (28%) had the mutation. Dr. Irene Roberts of the MRC Weatherall Institute indicated that this latter number was a "very high frequency."

In patients with the mutation, 7 (5%) developed AML at a median age of 16 months; no patient without the mutation developed AML. Among the 130 neonates with the mutation, 42% were considered to have "clinical" TAM and 58% were considered to have "silent" TAM. Researchers had predicted that babies with clinical TAM would have more severe disease, which turned out to be the case.

According to the study, newborns with Down syndrome are more likely to survive without leukemia if they have silent TAM, compared with those who have clinical TAM, and if they have an estimated variant allele frequency above 15%.

Source: MDedge.com, January 4, 2019

Vaxelis, a Pediatric 6-in-1 Vaccine, Receives FDA Approval

The FDA has approved Vaxelis (diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, haemophilus b conjugate [meningococcal protein conjugate] and hepatitis B [recombinant] vaccine), the first hexavalent vaccine available in the U.S.

Vaxelis, developed by Sanofi and Merck & Co., is for children aged 6 weeks through 4 years old to prevent diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease due to *Haemophilus influenzae* type B. The vaccine consists of a 0.5-mL intramuscular injection series administered to children before they turn 5 years old.

Vaxelis is contraindicated in children with a history of severe allergic reaction to a previous dose or any ingredient of Vaxelis, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, or *H. influenzae* type B vaccine.

The vaccine is also contraindicated in patients with a history of encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within seven days of a vaccine containing pertussis, which is not attributable to another identifiable cause, and in patients with a history of progressive neurologic disorder until a treatment regimen is established and the condition is stable.

Reported adverse reactions included irritability, crying, injection-site pain, somnolence, injection site erythema, decreased appetite, fever ≥ 38.0° C, injection-site swelling, and vomiting.

Merck and Sanofi are currently increasing supplies of Vaxelis to meet anticipated U.S. demand, and plan to launch the vaccine in 2020. The vaccine, which will be supplied in a single-dose vial in 10-count packages, was first approved in Europe in 2016.

Source: FiercePharma.com, January 2, 2019; Sanofi, December 26, 2018 ■